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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,907	06/15/2001	Harold G. Brown	2059-0106P	7324

2292 7590 07/08/2003

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EXAMINER
KHARE, DEVESH

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 07/08/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/631,411	08/03/2000	Xu Cao	D6258	9593

7590 06/03/2003

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McGregor & Adler LLP
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EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/880,907	Applicant(s) BROWN ET AL.	
	Examiner Devesh Khare	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's Amendment and remarks filed on 2/25/03 on paper no. 12 is acknowledged. New claims 27-30 have been added. Currently, claims 1-30 are under examination. Rejections of claims 1-26 under 35 U.S.C 102(e) as set forth in the previous office action are withdrawn in view of applicants amendments of the claims.

Response to Arguments

Applicant's arguments filed on February 25,2003 traversing the rejection of claims 1-26 under 35 U.S.C 103(a) have been fully considered but they are not persuasive. Applicants claim that "Lowry reference (U.S. Patent 4,900,550), there is no anticipation or prima facie case of obviousness since the ingredients in the Lowry reference are not present in a pharmaceutically effective amount and because the claimed use is nowhere disclosed in Lowry". Regarding Williams reference, Applicants presents the argument that "5-fluorouracil is a drug for battling cancer. No other drugs are suggested."

However, the use of essentials oils to increase the permeability of a cell-penetrating component or drug into the skin is inherent within the teachings of Lowry and Williams. Regarding Lowry reference, applicants are referred to col. 1, lines 54-62, wherein the cosmetic formulation containing a cell-penetrating component with the essential oils for accelerating the cell renewal cycle of skin to provide healthier, younger looking skin is disclosed. Lowry discloses in col.3, lines 50-69 and col.4, lines 1-15, the cell-penetrating component of the cosmetic preparation containing hyaluronic acid (0.09-0.11 wt%) and sweet almond oil (0.09-0.11 wt%). It is noted that the applicant's claims the use of essential oils between the ranges from 0.5% to 20% vol/vol with the complex

carbohydrate between the ranges from 0.1% to 99% wt%, in a method for effecting transdermal migration of a macromolecule. Use of a known member of a class of materials in a process is not patentable if other members of the class were known to be useful for that purpose, even though results are better than expected.

Williams reference discloses in the abstract the essential oils such as from Eucalyptus are very effective to increase the drug permeability into the skin. Williams reference discloses the studies that essential oils and their terpene constituents can be used as for safe penetration enhancers to aid topical drug delivery (see page R8, col.2, last para.).

Applicants argue, "the Lowry reference is directed to a cosmetic composition. There is no motivation for modifying the teachings thereof and converting the cosmetic composition thereof into a pharmaceutical composition." This is not found to be persuasive because the motivation for doing so is provided by Lowry reference, which suggests a cell-penetrating component containing the essential oils and complex carbohydrates for use in the treatment of dry skin (see col.3, lines 37-38).

Rejection Maintained

Rejection of claims 1-26 under 35 U.S.C. 103(a) is maintained. New claims 27-30 are also rejected under 35 U.S.C. 103(a) as being unpatentable over Lowry (U.S. Patent 4,900,550) in view of Williams et al. (*Int. J. Pharm,* vol. 57: R7-R9), as already applied to claims 1-26.

In claim 27-30, applicants claim a method for effecting transdermal migration of a macromolecule or promoting granulation of wounds comprising applying a

pharmaceutical composition which comprises at least one complex carbohydrate selected from the group consisting of oligosaccharides, sialylated oligosaccharides, polysaccharides and glycosaminoglycans, and at least one essential oil. Since claims 1,3 and 11 includes the possibility of using the same methods with at least one complex carbohydrate and at least one essential oil, claims 27-30 are obvious within the prior art already set forth in the rejections of claims 1-26.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowry (U.S. Patent 4,900,550) in view of Williams et al. (*Int. J. Pharm,* vol. 57: R7-R9).

The applicant's claims are broadly directed toward affecting transdermal migration of a compound by mixing the compound with an essential oil. Claim 2 place further limitations as to the nature of the compound (i.e., a complex carbohydrate).

Further limitations in the applicant's claims include specific ranges for the amount of essential oil (from 0.5% to 20% vol/vol, claim 4), degree of purity of the complex carbohydrate (concentration ranging 0.1% to 99%, claim 21), and scope of the complex carbohydrates and essential oils used.

Lowry teaches the use of several different types of macromolecules and complex carbohydrates in combination with essential oils, which is readable upon the scope of

the applicant's claims. The compositions disclosed by Lowry include the hyaluronic acid in an amount of 0.09-0.11 wt.% (col. 4, line 13) and sweet almond oil in an amount of 0.09-0.11 wt.% (col. 3, line 67).

Lowry differ from the applicants invention primarily in the scope of complex carbohydrates/essential oils used, the Lowry composition contains hyaluronic acid below 0.3 wt.% and essential oil below 2% vol/vol. However, as Williams et al. disclose, it was well known at the time the invention was made that essential oils were useful as skin penetration enhancers and a wide variety of compounds could be used with essential oils for transdermal penetration (summary and Table 1).

Therefore, when taking the invention as a whole, the use of an essential oil with a macromolecule/complex carbohydrate would have been obvious to one of ordinary skill in the art. Since Lowry teaches the use of several different types of macromolecules and complex carbohydrates in combination with essential oils and Williams et al. teach that the essential oils were useful as skin penetration enhancers and a wide variety of compounds could be used with essential oils for transdermal penetration, one skilled in the art would have a reasonable expectation for success in combining both references to accomplish a therapeutic composition comprising combining the essential oils useful as skin penetration enhancers and a wide variety of compounds for transdermal penetration.

2. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Devesh Khare whose telephone number is (703)605-1199. The examiner can normally be reached on Monday to Friday from 8:00 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, Supervisory Patent Examiner, Art Unit 1623 can be reached at 703-308-4624. The official fax phone numbers for the organization where this application or proceeding is assigned is (703) 308-4556 or 308-4242.
Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Devesh Khare, Ph.D.,JD(3Y).
Art Unit 1623
June 30,2003

ternational Journal of Pharmaceutics, 57 (1989) R7–R9
Elsevier

IJP 10007

Rapid Communication

Essential oils as novel human skin penetration enhancers

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(Received 10 October 1989)
(Accepted 16 October 1989)

Key words: Transdermal administration; Penetration enhancer; Essential oil; Terpene; Fluorouracil, 5-

Summary

Essential oils were evaluated as penetration enhancers towards 5-fluorouracil using excised human skin. Eucalyptus a chenopodium were found to be very effective, causing a near 30-fold increase in the drug permeability coefficient. Ylang ylang w mildly effective (8-fold increase) and anise had little activity (3-fold increase).

Transdermal delivery of drugs promises many advantages over oral or intravenous administration, but human skin provides an effective barrier to the permeation of most drugs. The principal barrier to topical drug delivery is the stratum corneum, the outer most layer of the skin comprising keratin-rich cells embedded in multiple lipid bilayers. In recent years much interest has been focused on methods of increasing stratum corneum permeability, and one approach is the use of penetration enhancers (or accelerants). These agents partition into, and interact with, the stratum corneum constituents to induce a temporary, reversible increase in skin permeability. We have investigated the penetration enhancing activities of some essential oils towards the permeation of 5-fluorouracil (5-FU), chosen as a model polar penetrant, in excised human skin.

The essential oils selected were chenopodium, eucalyptus, anise and ylang ylang. Oil of chenopodium has been used as an effective anth mintic, and contains approx. 70% ascaridole, well as *p*-cymene, α-terpinene and l-limonei Eucalyptus oil has been employed in ointments a topical counter-irritant and, together with m thol, as an inhalation. Its chief constituent is 1 cineole (approx. 80%) although it also conta α-pinene and small quantities of other terpe such as phellandrene. Anise oil provides appr 85% anethole and is an established flavouri agent used in the manufacture of liqueurs a dentifrices. Oil of ylang ylang yields geraniol a linalool esters of benzoic and acetic acids, toget with *p*-cresol methyl ether and other terpenes. is employed as a delicate fragrance agent and l recently found use in aromatherapy. Due to popularity of these essential oils their toxicities well documented (Opdyke, 1974–1976), and relatively low compared to most synthetic penet tion enhancers.

The activities of the essential oils were evalua using excised human epidermal membranes p pared by a heat-separation technique (Kligm and Christophers, 1963; Goodman and Ba 1988). The skin samples were fully hydrated a

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placed in stainless-steel diffusion cells, comprising stationary donor and flow through receptor compartments, mounted on an automated diffusion system (Akhter et al., 1984). Aliquots of 150 μl of a saturated, aqueous radiolabelled 5-FU solution were placed in the donor compartments and samples of receptor solution were collected periodically and the drug determined by liquid scintillation counting. At pseudo steady-state diffusion, the permeability coefficient (K_p) of the drug in the tissue was evaluated. The drug was then washed from the donor compartments and replaced with samples of the essential oils. After a 12 h treatment period the oils were washed from the donor compartments and replaced with the drug solution; the permeability coefficient at steady state was re-evaluated. An enhancement ratio (ER) may be used to define the activities of the oils;

$$ER = \frac{K_p \text{ after accelerant treatment}}{K_p \text{ before accelerant treatment}}$$

The enhancement ratios reported are mean values, from a minimum of five replicates, using 12 different tissue samples. Human skin permeability shows inter-sample variations; the experimental technique employed each piece of tissue as its own control thus minimising errors due to this phenomenon. Expressing the activities of the oils as the mean of individual enhancement ratios given a more accurate estimation of penetration enhancement than a simple ratio of the mean membrane permeability coefficients before and after accelerant treatment.

The oils clearly increased drug permeation across the skin as illustrated in Table 1.

The most effective oils were eucalyptus and chenopodium containing primarily 1,8-cineole and ascaridole, respectively. Both these chemicals are polar oxygen-bridged terpenes, 1,8-cineole being a cyclic ether and ascaridole a cyclic peroxide. Oil of ylang ylang shows less penetration enhancing activity towards the polar drug 5-FU, with an enhancement ratio of approx. 8. This oil contains oxygen-linked molecules with its terpene ester composition. The least effective essential oil, anise (ER approx. 3), contains primarily anethole, a chemical containing a methoxybenzene structure.

TABLE 1

The mean permeability coefficients (K_p) and enhancement ratios with standard error of the mean, of 5-FU in human epidermal membranes at 32 ± 1°C before and after treatment with an essential oil

Essential oil	K_p (cm/h) ($\times 10^5$)		Enhancement ratio
	Initial (control)	Treated	
Anise	2.30 ± 0.34	6.33 ± 0.50	2.8 ± 0.6
Ylang ylang	3.79 ± 1.25	29.6 ± 9.90	7.8 ± 2.6
Chenopodium	4.33 ± 1.32	93.5 ± 29.1	33 ± 8.0
Eucalyptus	2.09 ± 0.42	69.3 ± 13.4	34 ± 8.9

The importance of these chemical configurations in determining the penetration enhancing activities of these oils is, however, yet to be proven.

Some essential oils and their terpene constituents have recently been investigated as potential penetration enhancers. Eucalyptus oil and camphor increase the total flux of nicotine permeating excised hairless mouse skin (Nuwayser et al., 1988), although this animal is a suspect model for human in vitro skin (Bond and Barry, 1988). Terpineol and acetyl terpineol, prepared as the acetone extract of cardamon seeds, enhance in vitro diffusion of prednisolone through hairless mouse skin (Yamahara et al., 1989), and the percutaneous absorption of indomethacin has been promoted by the use of limonene and related compounds in rats (Okabe et al., 1989).

Clearly, further studies are required to isolate the active constituents of these essential oils, and investigations of the accelerant activities of the wide variety of naturally occuring terpenes and terpenoids may prove profitable. This study has shown that the essential oils may offer a large and useful selection of relatively safe penetration enhancers to aid topical drug delivery.

Acknowledgment

The authors thank the Science and Engineering Research Council for a studentship for A.C.W.

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